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Accn.

gt**cc**gtagtt agagggtgg ccttaataac ас<mark>СС</mark>ддаддд gagctaactg gag<mark>CG</mark>agacc Gccaccacc ccc**CG**aaaac cccccggct cagccttgac accecagt ce CGaggatgCG ccctccCGg ggtggtgttt t**CG**gg**CG**gct gg<mark>CG</mark>ggggaa GtCGccccac cttcctctgc ttctatccct **cc**gggctttc atctctgggt agggacctat ctggatctta gggtCGtatt tggggggtga caggg<u>cG</u>ct agaaatagga ggatggaggg ctgctgttct ggagggagg ctcacctctc agaggaaga <u>G</u>agcagggga ggctctgctC gggagagagg ccctcccct gg<mark>CG</mark>gacttc cctgtaaaga CGcagacacc <u>G</u>gagggt<u>CG</u>g tCGccccctc GtggcCGctg aggaaggggt GctgcacCCC Gaggatcaca cctccctct tccctttaat tttcactta cctacattc catgaccttt aaagttgga GCGgtggggg CGcagcacat attagagggc gt<mark>CG</mark>ggccag attgaaagga gcagcccCGa catgcaggct agg<mark>CGCG</mark>ggg **G**gagaagag<mark>C</mark> tctctctgcc gatCGtatct ggaa<mark>CG</mark>ctct CGacCGtgct aaagcagga gCGCGaaacC **G**gccctaga<u>C</u> ctcCGgggaa gtttctgct<u>c</u> aatccctcac ccacctcag ttttcctg<u>c</u> ccacctctc Gttgttctgg acttcaggga agataatcta cctcccttat ttgaagaagc accaaaggg<mark>C</mark> tgccagcttg aaaca<mark>CG</mark>atg cttcctaata aatgagtgaa gggcccctgg tgaagttgg gagggagag cagag<mark>CG</mark>ggg gccagtgag cttcagag<u>c</u> ctccaccttc ggaggtcagg aggc<mark>CG</mark>gg Gtgtcagggc ggcctcatgc aa**C**Gccacca atccgtgtgg gcagagtgag agc<mark>CG</mark>gacct aggaag<mark>CG</mark>gg **G**gcctg<u>CGgC</u> cagaaggga<u>c</u> aggaacacag aaaatcaccc cccatcttc aggatc<mark>CG</mark>tt gtgaaatac GctgcaCG ŬΙ \mathbf{a} gggacCGCGt acacctacag tgcctgtc<u>**cG**</u> aaggaggag gaggaggaac ttg<u>CG</u>tcac<u>C</u> ggaggac<mark>cG</mark>g aaacccttt ctcccttctg gccaaaggaa GttagagcaC gaggtgaaga agaaagcctg tgcagggg<mark>cG</mark> CGagCGtgga agaaagctgc ccctgcccc<u>c</u> gagcccccag acccccttc cagggggggg **CG**aagttatc gctattttct tctgaggtca caggaggatt gtctctcccc ttcctcctgg ад<mark>СС</mark>адддд caCccatgo **CG**ggaggaag tcaaggatg**C** ttggCGtgct ggggtgg<mark>CG</mark>g tttgtgggt gagagggaa gaggaaaggg cccagccagc caatcctCGc agttttaagg ccctattta aaaaacagaa ggcdatcgag gg<mark>CG</mark>aaggac gctcccaggg gCGcaggggg gccatttcct tgtcagcaga cccctgggag дддссс<mark>СС</mark>аа ccagagaagc acacactctg gaaacagctt atg**CG**aggtt ttctaaattg aatacaaggg gagct<mark>CG</mark>agc 1021 1081 1141 1201 1261 1321 1381 1441 1501 121 181 241 301 421 481 661 361 541 601 721 781 841 901 961 61

FIG. 1A

BP

MSP Unmethylated

APPLICANT(S): Sukumar et al.

TITLE: ABERRANTLY METHYLATED GENES AS
MARKERS OF BREAST MALIGNANCY

Application No.: 09/771,357 File Date: January 26, 2001

Docket No.: JHU1630

2/22



GT TATGTTATGT TTGTTGTATG	ce st	-	orward	Forward UM 22 BP MT 56	(SEQ ID NO:21)
T AAAATCCACC AACACAATCA		Reve	rerse UM	1 21 BP MT 56	(SEQ ID NO:22)
MSP METHYLATED 276 BP					
TAC GTGTTAGGGT CGATCG	F M 19 BP	MT 58	(SEQ ID	ID NO:23)	
CGA AATATCTACG CTAAACG	R M 20 BP MT56 (SEO ID NO:24)	P MT56	(SEO ID	NO:24)	

FIG. 1B



ID NO:106

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gcaccttcCG gggaaaggag GgCGCccaC tggaactcaa gcatgcccc a<u>CG</u>gacctag attgctgctg GacCGcttcc gaaat<mark>CG</mark>ccc aaactttcCG agg<mark>CG</mark>ggtgg attgttagac cagacacctc tcctataaaa GtccagcCGt ctcc**cc**cctc cctcctgctc tgg<u>CG</u>ggctg **CG**ct **CG**agag gagcaacagc caag<mark>CG</mark>gCGc ggg<mark>CGtCG</mark>ga tg**CG**ggctgt gagtc<mark>CG</mark>cag ccag**cc**cacc gccct**CG**gac cctctttCG **CG**ttgtagag cageceeeee gtttggcctt acttttcttg agctgttgcc aat**CG**gcccc agtctcctc<u>c</u> **G**g**CG**gggaag gggagga<mark>CG</mark>a tgctgcccc gg**cG**gctagg g**cc**gaaactt Gccdaactcc CGgggtgtgC teceetecee **G**gggggaagc caCGCGtCGc tccCGtcCGt aCGacagect GCGddddaGG gagCGggtgg tg<mark>CG</mark>ggag<mark>CG</mark> gcaagaagtc 6**90**6**90**6**90**6 tccccaCGct tgaacttctg cagactgggt **CG**caaatcct **ອວອວ**ວອວວ໓໓ CGCGgttgac cagcaatcca actgtgtaga tggccaggac CGcaCGctcC gaaggggag tgaatggttt ggactggaaa ccaatgacac tgcagctct<u>C</u> ggaggcctgg atccacac**CG** CG gaggtccc **၁**၁<u>၅၁၅</u>၁၁ ငင**်ငင်**အေရွှင် tCGCCGgCCG ag**CG**gcaagC **9**26**92**00666 ggcaag<mark>cGcG</mark> <u>G</u>gcagcagca atggccaa<mark>CG</mark> CGgaagatca cacCGaagag tggggag<mark>CG</mark>t caggc<mark>CG</mark>gga tgggtggctc ccccagccc gctgccac**c**G ctc<u>CG</u>ggctg gacatcaccc ggg<mark>CG</mark>ctgcc **GaCG**gggagg aggt<u>cc</u>ttt cctcagggcc **CG**ggggaggg tca**CG**tcagg cctccaagtc accettcca GccctcccCG **9**2066**9**200**9** ctgccc**CG**gg gcagc<mark>CG</mark>cCG GcagCGggtc ct<mark>CG</mark>ccagtc ccCGgcccag 26926926<u>9</u>2 CGCCGCGCtg ggttccttc Igcic a**CG**ccaggac ctttggatgt tcCGgatggg 266 1886 g**CG**g**CGCG**gg agctgcagaC gg<mark>CG</mark>agagag acctgaccat Igga ccacaccacc gg<mark>CG</mark>agatga tcc gag **5** gga S atc cct cag gca GcaCGgCGgg agc<mark>CG</mark>ggcag a<u>cc</u>agg<u>cc</u>t ggtataa tagggtt Ggaggaa **්**වට ටටටට ggaggtg tccctcc cagcac<mark>C</mark> ctttttg tccccCG GggcCGc ctcttct acctgc cagacCG cattggactg agggctcttg tcacagccad aggCGtagtc ccaccc CCCC ggcccagaag <u>G</u>tcttcagaa gggttCGtct tgggctgCGc 2092009292 aggaccegac ccCGaggaag aggCGcccCG cttCGaaaag gCGggctctg cctcccCGcc tctcctcCGC cctgca<mark>CG</mark>ga tggg<u>cG</u>cttt atcatgcagg gaggaagagc gg<mark>cGgCGaCG</mark> a<mark>CG</mark>agcagg<mark>C</mark> 9269263266 tcttaCGagg cagt**CG**ctga -61 121 241 301 361 841 901 961 1021 421 481 661 721 541 781 601 1081 1141 1201 1261 1321 381 1441 5

FIG. 2A



(Con't) NO:106 ID (SEO

ggctca<mark>CG</mark>ag gtc<mark>CGCG</mark>tcc aaggac<mark>CGCG</mark> cctctaccag cctggtccat agacctaggt acatCGactt gcagctatgt atggaggggg gcagggc<mark>CG</mark>g g<mark>CG</mark>gccaggt atggcaagct cctcaagctg ggactccaag cacccctca **G**gtctggagg agattcagac g**CG**a**CG**agct a**CG**ccttct**C CG**gagcccc **CG**gctcagct cactaccagg gtcctccaga aagctgagca 1621 1681 1741 1561

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21 BP AT 58 (SEQ ID NO:107)	20 BP AT 60 (SEQ ID NO:108)		20 BP AT 58 (SEQ ID NO:109)
FUM (3) 2	RUM (3) 2		FM (5)
tt TGgatggggt tgttatTGT	c ctaaccCAaa CAacCAacc	Methylated 200 BP	t tt <u>CG</u> gatggg gttgttatC

ID NO:110)

(SEQ

58

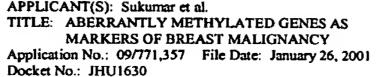
(4) 19 BP AT

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ctaaccCGaa

aaaCGac





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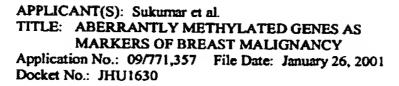
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RAR beta

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ინ**ეე**იია**ეე**ი a**CGC**Gag**CG**a ctgctt<mark>CG</mark>tc atgtaagggc ctctgaggaa taagaactgt gtgctttgaa ggagactt**CG** cacagagaag atacacca**CG** attcagtgaa tggtttcact catcctgatt aga<mark>CG</mark>gcctt cctgtgttc ccttctcagt agtagataag acccagcaag aagtgggaac cagtgctaaa ggtcagtcag **CG**gaaggct tttgccaaag gatgcCGaga tgggaaccc tgtacaaacc GgaaCGcatt agagcaccag gtcac<mark>CG</mark>aga cctgtgaggg Gactccagaa agaaaagaa tctgggacaa aa**CG**tctgcc tgga<mark>CG</mark>atct agctgggtaa cctgcctgga tgactttctc ctctgactga gaaaaaga<mark>CG</mark> cagaaacagg aacCGacaaa gatcaatgcc tcCGtagcat ccccaagttc aaaacagtgg gggtctattc tgaggactgg ggtaggatcC gggatcttc ggggtcag<mark>cG</mark> attgaaacac cccctCGag caatactgt<u>C</u> atttacactt gacaggaaca tcactctgcc gacctgggcc gagtttgcta ctgaaggc<mark>CG</mark> acagctgagt caagacacca ggatttggtc atcacagatc atggatgaca gaccttgagg atttatatca gaaattcctg gaacccttga agctcagtgg agaggcagga gccagctgtt gcac<mark>CGtCG</mark>g aggagaactt ggaaaatgca tccacttcct gaagaatatc gtaccactat gaatCGatgc ctatgaaatg tgtcaggaat aactttccct agtc<u>CG</u>actg taagat<mark>CG</mark>tg aattaccctg taccccagaa gcacaatgct gcctttggaa agac<mark>CG</mark>ccag agcactaaaa cttaatgaaa cttgaaaatg gaaggacat catctcaccc tgagctgttc Ü gtttgtctgg cag gga tcG tttacttgga gcccccatc tca gag Gagcaagcct tat gta aatcatcagg ccaaagaatc cca gat cct tgg gga gat ttc tac tag aga aagtcac gaagtat gcacaga ctcacca ctgacca agtgcat t**CG**caga gcaccag Gaactca accagct taatctg cattgct ttccaaa Gtgtaat tggagaa acagtcc tgcaata tagtaggaag aattcc ggggaccag tggattggcC tcCGagcagg ctCGtcccaa tttgcaagca tgccaggaca ttttcCGca gttattaata gtgggaatgt aagcaagaat aattccagtg ctggccacca ctacaagaac atc**CG**aaaag ggcttgacca accetaaatC acctttgcca gccatctgct ggtgcagag<mark>c</mark> cttagaattt cctcacatgt caagaaatgc acagcagagc tcaccactCG gtgacagaag 61 121 181 241 301 361 421 481 601 661 721 781 841 901 541 1021 1081 1141 1201 961 1261 1321 1381 1441

FIG. 3A





Unmethylated 163BP

ggattgg gatgt**TG**aga a**TGT** FUM 21 BP AT 60 (SEQ ID NO:92)

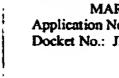
c Aaccaatcca acCAaaaCAa RUM 21 BP AT 60 (SEQ ID NO:93)

Methylated 142 BP

ga a**cccc**ag**cc**a tt**cc**agt FM (2) 19 BP AT 60

Gaccaatcca acCGaaaCG RM (2) 19 BP AT 58

FIG. 3B





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Homo sapiens AF024605 (SEC

7/22

cg O ctgcgcgggt gccactgtgg ccggacgact aaggcgaacg gcccgcgtc ggttgctggc ctccagcatc caacaacatg aggccccctg tggctctgcc latt taaagtcata cctgctgatc ggcaagcca gcctacc actctcccct cctctcacct gaagtggtgg agagcagtta gg cgt cccgtgcg b ag ccttcct cgcctct gtg cgcag b cgt B b tecetecet cctctccgc actctgggc atggcgc tctcgttcca ccatcctgcc gcggaaacaa agcagctccg atga tagtgccggg gcctgacctg gcgtggtcac accagtgcca cctggatcaa agtcggctga aaacatctcc tct gtgactctgg b atgttatgct tgaaatgcag agcctctg ttacccct tgactt Ŭ g b Ø age Q cct ggaë atg tg Ü g 1 D Q ggcgc cact ttcaacggcc cacgtctggg cctcc cttcagggcg ggctcaggcc gccaggcccg cagcccggag tacaacaagg ttctacctg ccttgccaga tcgtggggtg aaatacatgt gtactgaagc cggtcatcac gctgatccag cttcctccc actccccgct acatgtgt ccacacctct ctgcaaaatg ctgact g gccgcg Ca gat O gacco gtt ccg(Ct Q a gtgtgaggtc gggccaggac atgagagct gctgccgctg ggtctcgctc gctg g cacgcgcttg ggtgctgacg cctgctgctt gtaccaccag ccgctgtgct gcatcctc agagtgaag cgctcca cat ata gtg ccagatctgc ttcctctgcc cgtccatcct ccgccct ttctctgcct gccaggaagc ag ggcag gtttcct ρ b gctaaag T Q b gact D Q $\boldsymbol{\varphi}$ b D ag Ct Ct \circ Д accagagttg accagagttg tccatcccaa atctcatgtt agcttcccta ggccgcccg gactggaccg agaccttcca ctgtctacac gatccagatg gatccagatg gaggctccat gaggctccat cccaaaacga agccctggca ttccagagaa ccaacctgac ctgaacctca O O gttgtgagga aacaca tggcgaagc agatcctgg gaccaca gct a g gatgagcacg cgggccctgc ggcgactccc gcccgggctc cgcggctcgc gctcgagtag gtcctggtgg cgctctgttg tggggcacca actatcctga atatgtgctg cagcatccag gtctgtgacg cgctccaact cagatgccca tgtctgcact cattccccca caaaggttta ctggggtcac agtgccctct tcttagacat Q accagcggc gcgctgctc aaa atgtaa Ø Ø \mathbf{O} Ø 301 361 421 481 541 661 721 721 781 961 961 41 1021 1081 1141 21 01 12 12 \sim 7

TITLE: ABERRANTLY METHYLATED GENES AS Application No.: 09/771,357 File Date: January 26, 2001 Docket No.: JHU1630



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actg**cGcG**gg ggaccc**cca**a ctctCGttcc aca<u>CGCG</u>ctt ID NO:95) cttcaacGgc (SEQ cccaaaacc +349 लि GCGCGgctCG cagccctggc aggtctCGct gggtgctgaC GgcCGCac TGCGgaaaca Q +169 c<u>CG</u>cagagg<u>C GgCG</u>ctgctc nts Sequence analyzed: Exon 3 sequence

gaccagagtt

tgtcctggtg

ccccetaccc

gcctatgg**c**G

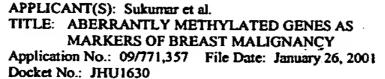
Unmethylated 128 BP

(SEQ ID NO:77) 56 AT ВР FUM 20 Nesl trGtagaggr GgrGttgttt ID NO:78) (SEQ **2**6 AT ВР 22 RUM Nes1 acca aaaaCAaaaa CACAcaat

BP 137 Methylated

ID NO: 79) (SEQ 56 AT BP 20 FM Nes ctCGaa gtttatggCG tttC

80) (SEQ ID NO: 58 BP AT 20 Nes1 RM t tatttcCGca ataCGCGAC





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gtt ည် cttg CG cat CGC tct ည် cat ctg S agctcatttg tagcaccctt ctccta**CG**ta t<u>CG</u>taaatcc ggagg<mark>CG</mark>agg cagc<mark>CG</mark>gact D T b p p p CGgCGggg ct O acacata gcaa B Ď. **CG**gagtg gcaa Q Q agggcai ttaggg CGCGt S g<mark>CG</mark>ca(D cta Ga tat Ct D tgc gca aa ctccctct a<mark>CG</mark>gCGgagc tacctgggct gc gagccaaagt acttggttcc tctccataat acaaaataag gttgtccag gagttgggt tgc<u>cccc</u>tt 9 c**CG**ac**CG**ddd gtg<u>ce</u>tct cattt à Ü ccctacct ပိုင္တရင္သင္သင္သ ctggagt cttatgt Ü GgctCG(GCC) attg b ت b GgctcCGgaC CGaggCGcCG CGagggggcc CGCCGggctC <u>ce</u>gctggctg GCGctctcCG gtagcCGtag **G**gaactatga aaatgagttt agt gctt CGCGgtCGtt aatt ccGat ca<u>CG</u>tgcttt cactaatagg accat g tgggacat b ວວ<mark>ອ</mark>ີວວອີວ g CGccca Q b ğ Ď tggc gct 1 \mathcal{D} t tggc 1g**CG**g CGtcctcctC <u>cegcetceg</u>c CGctgcCGgg tgga<mark>CG</mark>tggc .gctg<mark>CG</mark>gg<mark>C</mark> catgccatt ctCGctcaC g<mark>CG</mark>ac<mark>CG</mark>ca gaaatgac atttgtggct CGCGtgcc actt<u>CG</u>aat aact**CG**tg ggctcat Ø ccatt b Ü Q $\ddot{\mathbf{y}}$ aaaggc U ddd**CC**d מ b $\ddot{\mathbf{o}}$ g ğ ğ Q ğ Ø D. Q d U g b Q Ü O ggagagtg<mark>CG</mark> ctggcag<mark>CG</mark>t a**CG**ctgagat tgggtgctgc tggtggctgt ggatttagaa atctggggtt ctggcagggg tccctgaatt ccatttggat tgtgtgcttg tgatgaatta tatggggta<mark>C</mark> cctctagagg Ø cccctggag g attgaggt taccaat actgg 9 gctgctgatg tttcc<u>CG</u>c<u>CG</u> CGagCGgcCG gctCGcCGag accaagagag gcegtcecet ccaggggtag ctgct**CG**ctg CGCGctggCG at<mark>CG</mark>ggctga gtagtc<mark>CG</mark>gg ttttttgata gcacaattta ggcacccaaa tgcctgatga ggggtgg<mark>CGC</mark> CGagCGccac c**CG**ggggt**CG**a taggat ىد at D b Q 710. 7161 221 281 .6681 .6741 .6801 .6921 .6981 .7041 .7101 .7161 01 662 9 マ 64 S Ó Ó

FIG. 5A



gccagc**c**G D U aa<mark>CG</mark>g<mark>CG</mark>gca atgcactc**cG** tggtc1 cccttgcag b ccCGgactac CGaag ctaat tag U tcat tati ctti to ŭ ğ ù aa O U d Ü d d 97 U agtc<mark>CG</mark>gctg acccaactcc t**CG**accc**CG**g ct**CG**g**CG**agc agcccaggt ggctc<mark>CG</mark>gcc caagcacaca caattggta aaagca**cc**tg gtcatttcca atccaaatgg nts analyzed: aa gtggCGctCG taacktcaat .cctCGcctcc CGgcCGctCG **၅၂၁၅၂**၁၁**၅၂**၆ aattcaggg ctggacaaca acatgtccca agccacaaa g CGgt CGct gaccg region ت atctcag<mark>CG</mark>t CGccagCGCG at CGg cag ct cctccag**c**g GCGccaccc aacGaccGCG taatgggctg <u>G</u>tgat<u>CG</u>agc tcatcaggcaggatttaCGa ggaaccaagt 97) Promoter aactcattt ಥ aatggcatgg a**CG**ctgccag tcagcc**CG**at tg CG Sa <u>29292</u>666<u>92</u> tcatagttc<u>c</u> taga<mark>CG</mark>caca tttgggtgcctaCGtaggag cttattttgt tcagcc**CG**a Ceggacece aattttgc atgagccc 3' (SEQ ID NO aagggtgcta gcatcctCGc aagctggg**c**G gaaatgcaat ggca<mark>CGCG</mark>cc cctctagagg attatggaga cta CG gctac GccCGcagct CGcactctcc tatcaaaaaacaa<u>atg</u>agct t 0 2 Complementccaatcctct aactgCGagg actgg**CG**g**CG** Gtacccata taaattgtgc ccccegtceg cagttgcata caccagttta gcaggtaceg CGgagagCGC gccaCGtcca

FIG. 5B



APPLICANT(S): Sukumar et al.

TITLE: ABERRANTLY METHYLATED GENES AS
MARKERS OF BREAST MALIGNANCY

Application No.: 09/771,357 File Date: January 26, 2001

Docket No.: JHU1630

11 / 22

UnMethylated 213 BP

tregtreg aagttgggre FUM 18 BP AT 56

gtaTGtg attTGaagtT Gtatt

aataC AacttCAaat caCAtac

56

AT

BP

22

Methylated 183 BP

tttagcgg tggCGttcg FM 18

58

AT

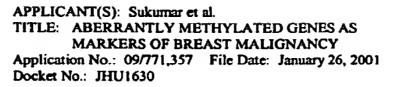
BP

taccatg attccaagtc Gtat

ataC GacttCGaat caCGta RM 20 BP AT

26

:1G. 5C



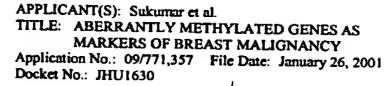
MAR 2 2 2004 C

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Sequencing 307 BP

attttgtta taatgggttg taat	Hox A5 Seq. F 23 BP AT 56 (SEQ ID NO:73)
ggag ggaattaagt atatgtt	(SEQ ID NO:100)
aacatat acttaattcc ctcc	Hox A5 Seq.R 21 BP AT 56 (SEQ ID NO:74)
Expression 248 BP	
tcattt tgcggtcgct atcc	HOX EXP F 20 BP AT 60 (SEQ ID NO:75)
ccaggta cagccagccg gc	(SEQ ID NO:101)
ge eggetggetg tacetg	HOX EXP R 18 BP AT 62 (SEQ ID NO:76)

FIG. 5D





romoter and gene, complete cds.

Homo sapiens 14-3-3 sigma protein p

ACCESSION No. AF029081 (SEQ

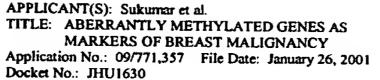
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FIG. 6A

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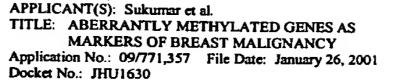
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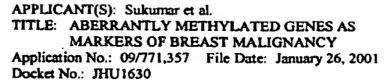
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FIG. 6C





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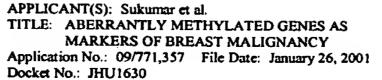
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FIG. 6D





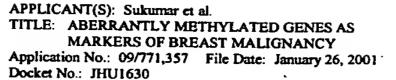
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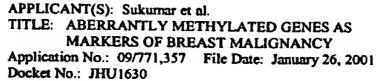
FIG. 6E





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FIG. 6F





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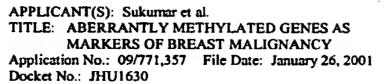
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H.sapiens Wilms tumor (WT1) gene promoter

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¥ O U ർ D O ŧι D D Ø ർ D Ø Q O Ø U Д D \mathcal{D} O O Ø D U D O O O ىد ιt b \mathbf{O} D d \mathbf{O} ർ \mathbf{O} D \mathbf{O} L T \mathbf{o} \mathcal{D} ർ ಹ D O \mathcal{D} O Ŧ \mathbf{O} ¥ O Ţ ൯ Q U \mathbf{O} O ർ \mathbf{O} \mathbf{c} \mathbf{O} U 4 ർ ¥ U \mathbf{o} 4 O Ţ ಗ T O 4 đ Q 4 O Q p p t מ O U ៧ u Д O U ർ 4 D D \mathcal{O} O 1 U O \mathbf{O} O \mathcal{D} Ø O g g O Q u מ 4 Ø Ø \mathbf{O} O b g U מ \mathcal{D} U b O U O O מ a O U b Ø Ţ O Q T Q ಹ U D Ø \mathbf{O} מ g T ៧ g Ø Q \mathcal{D} U a U U U b O b Q ಹ Ø b $\boldsymbol{\omega}$ מ \mathcal{D} \circ U b ർ D 4 b D U U b U g b a g b U D D g U O Q u g Q 1 U g ർ b b 4 4 D D D Q $\boldsymbol{\mathcal{Q}}$ Ø D D Q ര U U ന O \mathbf{c} U ര ൯ U ಹ O \mathcal{Q} O ർ O U C O O ർ \mathbf{c} d ർ ಹ Q O b ิต Ø b g Ö 4 ർ b U O b מ O ൯ ന Ø Ø U U u O Ø Q ¥ g \mathbf{c} Ţ ¥ g D g b ര D \mathbf{O} Q Q Ø Ţ \mathbf{c} \mathbf{O} Ü g 4 O \mathbf{c} 4 T ಹ \mathcal{D} O \mathcal{D} O \mathbf{c} φ O D u b 4 4 O B Ü 4 Q O D \mathcal{Q} \mathcal{D} D O \mathcal{Q} b O ന \mathbf{c} C $\boldsymbol{\varphi}$ g Q 4 b O Q ന ർ \mathbf{O} ಹ \mathbf{O} D Д D O D a \mathbf{O} Ţ ಹ b Ţ \mathbf{c} \mathcal{D} Ø T) O \mathbf{O} Ø b b \mathbf{O} ൯ \mathcal{D} b \mathbf{O} U O Ţ u \mathbf{c} р U ಥ b D U ىد 4 Q \mathbf{O} Ţ ർ Д D ത U Q U D מ O O a O U \mathbf{O} 4 b Ŋ b \mathbf{c} 4 ρ O D 4 4 Ъ O \mathbf{O} מ O D D u O 4 U \mathbf{O} 4 Q Q D מ U U מ \mathcal{D} $\boldsymbol{\sigma}$ O Ø D Ø U U b U \mathcal{O} O \mathcal{D} ത O Q b b U D b b b ൯ b d O O U t a 4 D D O \mathcal{D} D מ O D B b ൯ ¥ \mathbf{O} b מ U ർ \mathbf{O} b O Ţ \mathbf{O} \mathcal{D} \mathcal{Q} b O U Ø $\boldsymbol{\sigma}$ O a מ U T 4 D U D u ಹ D U Ø Ø O מ ർ D ർ $\boldsymbol{\varphi}$ מ O O \mathbf{O} U D U b U ർ O \mathbf{O} \mathbf{O} ർ U ಹ U ർ Ø \mathcal{Q} D מ D O u ർ U O מ O \mathbf{c} T B T O O \mathbf{O} T O U ർ ർ D מ \mathcal{D} Q O U U T 4 O O ı O ർ \mathbf{O} \mathbf{O} \mathbf{C} D 4 ർ D Ø g O D \mathbf{c} \mathcal{D} b b O O đ \mathcal{D} $\boldsymbol{\sigma}$ Ø Ø O 4 Q D D \mathbf{O} ಹ a מ D g ىد \mathbf{O} T $\boldsymbol{\varphi}$ g g t ¥ 1 ര U D Ø g ർ ര a Ø Ø Ţ ಹ ർ ب b \mathbf{O} O b Ø \mathbf{O} D \mathbf{O} ർ ൯ D Ø ൯ φ מ D U \mathcal{D} O \mathcal{D} \mathcal{D} מ U D \mathcal{D} U מ O \mathcal{D} $\boldsymbol{\mathcal{Q}}$ ത σ ർ ർ O $\boldsymbol{\varphi}$ O $\boldsymbol{\mathcal{D}}$ \mathcal{D} O מ \mathbf{O} O \mathbf{c} Ŧ $\dot{\mathbf{U}}$ ¥ Ţ b U a \mathbf{O} O Ø L \mathbf{O} g b $\boldsymbol{\mathcal{Q}}$ b Q D b \mathbf{O} U O 1 \mathcal{O} g a O ಹ D D \mathbf{O} ർ Ø U U $\boldsymbol{\mathcal{Q}}$ מ Q ര O U \mathbf{O} ಹ Ţ T Ø ര \mathcal{D} U ¥ ಹ U T 4 \mathbf{O} D O U ಹ \mathbf{O} Ø b U ത ಹ D \mathbf{O} U b \mathbf{O} O \mathbf{O} b D b ಹ \mathbf{O} Ţ b Ø g b b O U u b Ţ U ർ O \mathbf{O} D מ \mathcal{D} b \mathbf{O} b T D \mathcal{D} ർ ىد 4 O an U ದ Q 4 U O \mathbf{O} O U \mathbf{O} \mathbf{O} ಹ O \mathbf{O} O U D U \mathbf{O} U ർ O ಹ O ർ b ı O \mathbf{O} \mathbf{O} \mathbf{O} \mathbf{O} b U O D D U ർ Ø Ö Ţ Ø ι O ಹ ¥ ർ b 4 ಹ \mathbf{c} Ø Q ർ ಥ U O D \mathbf{O} O b b \mathcal{D} ർ g \mathbf{O} 1 מ g O b O b g ർ b ർ \mathbf{O} ർ Ţ Д O \mathcal{D} \mathbf{O} O 4 O D 4 \mathbf{O} 4 $\boldsymbol{\varphi}$ O \mathcal{D} ည \mathcal{D} O O മ \mathbf{O} Ö g g ಹ Ţ b Ø O O \mathbf{O} ದ b \mathcal{O} T T \mathbf{O} ർ \mathcal{D} U D to O \mathcal{D} T 4 ന ส ಹ cgcttctt Ø gccct ctgctcccac gatggagg atcactga agcctacc accgcatt cagattt บี b acgcacc ttcccaa cgcccca gctccag tccccaa aaccgct Ţ cccggct tccccta gag CCC caagggt agatatt gcgcct cgacct ggg(ccca(g S 1 b ct \mathbf{O} ğ C Jgcgill, tagaagaatt Trogc cggcggagtg tcaccctcc gaaatacg gt \mathcal{C} O 1 U Q ata CCC ggccac b \mathcal{D} \mathbf{O} B שש ggtaggcggc tcgaaatacg Ŭ saagggtate ycctcttgg Q b t ccggc Q cgaagggag cccgtgggc ctcctggtc b p n ccctcccg Ţ g Ø acg D O g yggattti :aggggtt regttt g acccct cta gcc Ct \mathcal{D} \mathbf{O} ctt d ag b Ç 1 ğ g O ď Ü ρ \mathbf{O} O ag ΰ gt Ĺ ct O Ø \mathbf{O} d t b \mathbf{O} \mathbf{O} \mathbf{O} O -----

FIG. 7A





D O ಥ \mathbf{O} D to to \mathcal{D} Q \mathbf{O} \mathbf{O} O \mathbf{O} D U D U U U D מ D D O D U \mathbf{c} b р ಡ Ü Ø 4 D Ø D T \mathcal{D} Ø Б \mathbf{O} O D \mathbf{O} D O U D O D O D S O ದ U D Ø ∇ \mathcal{D} ש מ O ർ ർ \mathbf{O} \mathcal{D} Q Q D Ø ർ Q O D U O Q a p U D b b Б O U ι \mathbf{O} 4 \mathbf{c} \mathbf{O} 4 ಡ \mathbf{c} b 4 4 d \mathbf{O} b מ D ർ \mathbf{O} \mathbf{O} \mathbf{O} \mathbf{O} \mathbf{O} \mathbf{O} \mathbf{O} D b \mathcal{Q} D ם ס $\overline{\mathbf{c}}$ g Ü a g Ø b O Ø 4 D Ø \mathbf{c} g O g U 9 Ø \mathbf{O} U T Ø O \mathbf{O} D Ţ Б מ \mathcal{D} ם ש g Д O מ ർ \mathbf{O} \mathbf{O} D ಹ D 4 U U ದ O \mathcal{D} ಹ D O O O \mathbf{O} O 4 שממ \mathbf{c} \mathbf{O} \mathbf{O} D b \mathbf{O} 4 b D Q U O b \mathbf{O} \mathbf{O} 4 4 4 U O O Ø \mathbf{O} b מ \mathbf{c} \mathbf{O} Д \mathbf{c} b D ם פ b \mathbf{c} b р b g 4 U Д B O U $\boldsymbol{\varphi}$ င်ဝ g Ø \mathcal{Q} \mathcal{D} Ü Ü D Ü D 1 \mathcal{D} U \mathcal{D} U Q \mathbf{O} p p a \mathbf{O} O $\boldsymbol{\varphi}$ \mathbf{c} D ര U \mathbf{O} Ø Q Q ಹ O b O U \mathbf{O} O U b g \mathbf{O} b \mathbf{O} 4 Ö D Д \mathbf{O} S ർ \mathcal{D} מ \mathcal{D} Ţ ש ש 4 \mathbf{O} \mathbf{O} O Q \mathcal{D} \mathbf{O} U U \mathbf{O} \mathcal{Q} Д IJ Q \mathbf{O} D D U \mathbf{O} Ø \mathcal{D} U O p q Ö \mathbf{O} U g g Д O O \mathcal{D} \mathcal{D} O \mathbf{O} Ŋ Д D O b \mathbf{O} Д Д g D \mathbf{O} \mathbf{O} b 1 d D 4 р \mathbf{O} \mathbf{c} \mathbf{O} O \mathbf{o} U g D G ρ Q pU Ø \circ ಹ U ಹ O Ţ \mathcal{O} g \mathbf{O} ρ U \circ Ø \mathbf{o} Д Ca \mathbf{c} O p T b \mathbf{O} 4 U \mathcal{D} C \mathbf{O} \mathbf{O} \mathbf{c} T g T Д \mathbf{O} \mathcal{D} D ಹ d ပ Д p p g b O Ţ Ţ O ם ם \mathcal{D} \mathbf{c} \mathbf{O} Ą Q Ø g b d Ö D a ൯ O \mathbf{c} \mathcal{D} Ø C Ü b Б g \mathcal{D} D \mathbf{c} מ \mathbf{O} \mathbf{c} \mathbf{O} U Q \mathbf{O} 4 שש g \mathbf{O} \mathcal{D} U U \circ Ö \mathbf{O} \mathbf{O} U D Ø Ţ 4 \mathbf{c} b \mathcal{D} g \mathbf{c} b O \mathbf{O} O \mathbf{O} \mathcal{Q} a d poU M U \mathbf{O} Ö ttcaaggca cttcccgcc agcccaggc ggacccggc ggtgtctga ggcgccgcc ggcgccggc ggagccgag cgcgccgcc ggagccgag ccacttttc tcctccgcc t 0 00 0 0 O Q S W 0000 ർ t O \mathbf{c} p n O O TO O p \mathbf{O} υσωσοσωσμού C D D g U p a c p a U B g U g る b t D Q S U U U D ರ th o p ΰ pτο τα τα το \mathbf{c} 406784067840678 4556678899001147

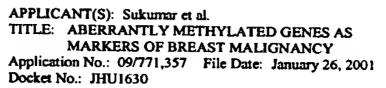
10

NO:

ID

SEQ

FIG. 7B



9 2

ID

(SEQ

4

AF19154

Number

ccession

region

promoter

dene,

beta

receptor

estrogen

ens

sapi

Homo

(ER):

Receptor

Estrogen

cds

and partial

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agtagaga<mark>CG</mark> **CGCG**atcttg cacctgcctc tttttttt ctcctgagta gaagctgatt gcatatgggg gcatgttgtc ctgcctcaag aatgaaaat gaagcagat Ø acaaccetca gce tactgtaaaa gcacagatgt ctgccaccag **CG**gagaaggg aggaagtacc tgagaaccca **G**ttgctgct aagtgtggtc gcatattctc tttcttcac **CG**gtttcca tcaacccag ccctggggc ttcattttc aatcagaca gt catct atagatgcat ctgcctcagc aagctgattt aatgcağtgg cct**CG**tgatc ttgtatttt gcctggccat D lag**CG**c actaacttct ctctcagctt gtttagctga ctcatcttta ctgaggctgg gatctggatc gattaattag tagtctCGca ggaactgggg agtgagtt**cG** tcttgagggc tactttcctt gtgcctccag c**cc**aggttac ggctccttag <u>G</u>tgatcct<u>CG</u> gttggaaat tccttcatg aggaggaag ctgagatt CGddd9 D D gctggtattg ag**cG**attctc tggttgaaat ccaccaaatg cccaggctgg cagccaattt aaactcctga gagccaccat taaggtggca agacagggag cacagctatt acctgtggac ttcCGtccaa gaaaccagga caccaaacag ctctattaga gtcacatgo tggtttgat actgtggtcc ttaagctggg ggtgggcag gccacttca cccagtgacc actccagggc ttcaccact ggctgagga<u>C</u> cccaggacct actgggggct CGctctgtCG caagtatata **GaCG**gcc**CG**g tgttggctta cccatgttca ccac**CGCG**tc ggctggtctc ttataggtgt attttctcca ccaggacagg caacctgaga tttggctaaa Gacacactct ggagacttt tgtcttcatt cctCGtcttc acctgagtag atggcctgtg gccagttaag gaacaccca c**CG**agaagag gtctccc**cG**g Gaaaggcctt gcctctctgg gtgagtcagg gt**cG**gcatcc aatctgag **CG**gctttgcc gtc gcc taa gtg **G**gaggcacag gatctaa**CGC** tct cct tca acc atcatttaac atttgccag<u>c</u> agtgctgaga ctctgccttt gtggggcagt ctttggagcc aaatgcccc Gtctctctat cccttatgcc ctgccttaaa Igg S Ø gt aa ctctagtcca at ct gggtctcac tgggtgag gggcctt caaaccca tgacactt ctgtatca ccagacct ctggcate tttttct gacagag a**cccc**tg acctcCG atcttgt atgttgg ttgagag ggccctact actatagggc gggg<mark>CGCG</mark>ag **CG**c**CG**tggc**C** ctcacctatc at tttttttga gctcactgca gctgggatta aggtttcacc ggcctcccaa tttttaaacc actgggtact gcacacttg<u>c</u> tgctgcagtt tggacttagg gacagggaga gcttctccat cttccctcc aaaaccatgt gacactgggg tcagcaacag cctgctgggg ctcctccac tgggatctt ggggatttga ctgttctgaa cccagactg ttccagag 481 541 601 661 721 721 781 901 901 1021 1081 1141 1201 1201 61 121 241 301 361 421 1321 1381 1441 1501 1561 1621

FIG. 8A



agaggtca**CG**

gctcccactt

gtt<mark>CG</mark>agggt

ccaggagt**c**G

ggtgga

tgtg

ccactatcct

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gggctcaggc tccttaagtc caCGtgtcCG cccc**cc**ccag tgcaggg**cG**a ggctctgggg ctttcctcaa ctcctacaac gccca**CG**aat ctcctatgta gaattacagc tcagctgtt tccgtcacct aaggggctta agctgCGaCG ggtgCGctCG g<mark>СС</mark>ддаааад gacacccact tcttgaaact aggtgttttc cattatactt attctccttc acataccttc ctgctgtgat gctccctggc taaaaggaag ggaccacc<mark>cc</mark> tggctttttg aataactgcc agctgcagga ccccctaat atctgcaagc tcttcttgca tctagcctta ttctatagcc Ggctccatat dddcc agac**c**GtcGg tctCGgtctt ctccagctgc ggctgCGaga ggc<mark>CG</mark>gggag GcCGggagac c<u>CG</u>gagcctg **CG**gtgtgttt cctttgtgcc cctggagcaC aaactcacca agccatgaca cttggaaggt gggctgg<mark>CG</mark>c **CG**ggg<mark>CGCGC</mark> 2525261 ttcctg ccctcc cagttt caag<mark>CGCG</mark>ga g**cc**agccdtg caaggc taatga cttacc tcgatataaa atatcc atgtcactaa **9**266 tcta tttt atgas atta ccato aagg agagcagg**CG** ctg**CG**ggggca caggtgg**CG**g CGCGGCGtCG actactccc **G**cttgtgatc gaggcagttg tctcaagada ctttgagaa<u>c</u> gattttagag tgcagtcaat gacagccacc attcccagca 1801 1861 1921 1981 2041 2101 2161 1681 1741 2221 2281 2341 401

BP 288 Unmethylated

2 2

NO:85) H (SEQ 9 AT BP ~ FUM agat<u>rG</u>trGg ggrettteg Ø

NO:86 H (SEQ ggttttgg agttgTGaTG 1G

NO:87) ΩI (SEO œ S AT Д 回 20 RUM ঠ CAtCAcaact ccaaaacc

BP 181 Methylated

NO:88) H (SEQ 9 Þ ВР 18 F gCGagCGt agagtagg<mark>c©</mark>

NO:89 (SEQ ID t tacctgttco **CG**ggaaag

9 AT ВР 20 图图 ctttcccG CGaacaCGta ಡ

ID NO:90)

(SEQ